British Journal of Venereal Diseases, 1978, **54**, 262–265

Recurrent genital herpes among women: symptomatic v. asymptomatic viral shedding

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SUMMARY To investigate whether asymptomatic shedding of herpes simplex virus occurs in women with recurrent genital herpes, six women with documented disease were followed up twice weekly with viral cultures and pelvic examination. During the study period of 1330 patient days and 452 patient visits, 26 episodes of genital herpesvirus infection were recorded. Twenty-three (88%) episodes were accompanied by signs and symptoms. Three (14%) of the culture-positive recurrences were asymptomatic. In one episode an asymptomatic lesion was noted, and in two instances viral shedding from the vulva or cervix occurred in the absence of visible herpetic lesions. Three of the six women had evidence of recurrent cervical herpesvirus infection. No relationships between menstrual cycle and sexual activity and the onset of recurrence were noted.

Introduction

Genital herpesvirus infection is the third most common sexually transmitted disease diagnosed at the Harborview Medical Center at Seattle. Previous studies on prevalence have shown that herpes simplex virus (HSV) is detected in the cervix in 0·6% of pregnant women (Bolognese *et al.*, 1976) and in 5·8% of female patients seen in a clinic for sexually transmitted diseases (STD) (Wentworth *et al.*, 1973). Seroepidemiological studies have shown that while antibody prevalence to either type 1 or type 2 virus varies with age, race, gravidity, and sexual experience antibody to HSV-2 is often found in patients without a history of clinical genital disease (Rawls *et al.*, 1970). These data suggest that genital HSV infection may initially be asymptomatic or mildly symptomatic. Cytological evidence of herpes group virus infection from cervical preparations often occurs in the absence of vulval disease (Ng *et al.*, 1970). Recent investigations have also indicated that cervical infection with HSV as demonstrated by either viral isolation or cytological changes in cervical cells was more often present in women with initial genital infection (87%) than in women with recurrent genital disease (4%) (Adams *et al.*, 1976). In addition, 206 routine cervical cultures obtained after the first genital infection had resolved revealed no evidence of recurrent cervical HSV infection (Rattray *et al.*, 1976).

To investigate whether asymptomatic cervical excretion of herpes simplex virus occurs in women with recurrent vulval disease and to quantitate the frequency and duration of asymptomatic viral shedding we prospectively followed a small cohort of women with documented genital disease.

Materials and methods

Six women (Table 1) with previously culturally proved genital HSV infection were investigated twice weekly for a mean of 32 weeks (range 13–48). At each visit each patient was asked about her sexual and menstrual activity; a pelvic examination was performed, and any sign or symptom suggesting herpesvirus infection was recorded. Cervical cultures as well as cultures of any other suspicious genital lesion were taken routinely. Additionally, routine sweep cultures of the vulval area were taken at 42 visits from women without lesions,

To isolate HSV specimens were inoculated on to human embryonic fibroblasts overlaid with Eagle's

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Received for publication 30 June 1977

Table 1 *Details of patients*

Data	*Case no.* 1	2	3	4	5	6
Age (years)	24	22	19	22	37	27
Race	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Marital state	Never married	Never married	Never married	Never married	Married	Married
Socioeconomic status	Mid	Mid	Mid	Mid	Mid	Mid
Occupation	Student, free-lance artist	Medical student	Student	Student	Housewife	Administrative assistant
Parity	G_0P_0	G_0P_0	G_0P_0	G_0P_0	G_2P_2	G_0P_0
Contraceptive method	Oral	Oral	Oral	Oral	Tubal ligation	Oral, subsequently husband had vasectomy
Previous STD	Yeast vaginitis	Yeast vaginitis	Trichomonal vaginitis	Trichomonal and yeast vaginitis	None	None

minimum essential medium containing 2% fetal calf serum, 6·6 mmol/l sodium bicarbonate, 100 μg/ml streptomycin, 100 units/ml penicillin, 10 units/ml nystatin, and 100 μg/ml gentamicin. Tubes were incubated at 37°C. Tubes demonstrating cytopathological characteristics of HSV were passed to HeLa cells to differentiate HSV from cytomegalovirus. The initial HSV isolate from each patient was typed by the immunoperoxidase method (Benjamin, 1974). Complement fixation titres were performed as previously described (Wentworth and Alexander, 1971).

Results

During the study period of 1330 patient days and 457 patient visits, 26 recurrences of genital herpesvirus infections were detected either by the appearance of characteristic vulval lesions or by a positive viral culture in the absence of lesions (Table 2). Of the 26 recurrences, 23 (88%) were accompanied by clinical signs and symptoms. Sixteen of the symptomatic recurrences yielded positive cultures of vulval lesions and negative cervical cultures. In two (8%) of the symptomatic recurrences, HSV was isolated from vulval lesions and the cervix. In five other recurrences, the patients presented with symptoms and lesions characteristic of genital herpetic infection, but the cultures were negative. The mean duration from onset of symptoms to viral sampling was 3·3 days in these culture-negative episodes compared with 1·3 days for those that were culture-positive [$P<0.05$ (t test)]. Thus, the negative cultures were probably due to the later sampling of the lesions and the short duration of viral shedding seen with recurrent genital disease.

Asymptomatic viral shedding was recorded in two of the six patients in the study and accounted for 12% of the HSV recurrences (14% of the culture-positive episodes). Asymptomatic vulval shedding was found twice during the course of the investigation. On one occasion the patient had no symptoms of vulval irritation, but a small 2 × 3 mm wet, vulval ulcer, unnoticed by the patient, was found on examination; HSV was grown from the lesion. It was then decided to sample routinely the vulval area of all patients at all visits in the future with a cotton swab and to submit these specimens for viral culture. One of these 42 subsequent vulval sweep cultures grew herpes simplex virus. The patient was without signs or symptoms

Table 2 *Frequency of asymptomatic v. symptomatic recurrences among women with genital herpes*

	Case no. 1	2	3	4	5	6	*Total*
No. of weeks followed up	47	46	31	29	24	13	190
Total recurrences	5	7	10	2	2	0	26
Recurrences with lesions and symptoms							
Vulva (culture-positive)	4	3	7	2	0	0	16
Vulva (culture-negative)	1	3	0	0	1	0	5
Vulva and cervix (culture-positive)	0	1	1	0	0	0	2
Recurrences without symptoms (culture-positive)							
Vulva with lesion	0	0	1	0	0	0	1
Vulva without lesions	0	0	1	0	0	0	1
Cervix without lesions	0	0	0	0	1	0	1
Frequency of recurrences (per 100 patient days)	1·52	2·17	4·61	0·99	1·19	0	1·95 (mean)
Months since primary infection	9	11	1	10	24	72	
HSV type	2	2	2	2	2	1	

at the time of sampling. A vulval sweep culture at the next visit, two days after the positive isolation, did not grow HSV.

Asymptomatic cervical excretion was found once during the course of the study. During the period between clinical recurrences 429 cervical cultures were taken when patients were without signs or symptoms. Of these only one (0·2%) was positive for HSV. The duration of viral shedding was short; viral cultures were negative at the next visit three days later. Neither signs of vulval or cervical lesions, nor symptoms of increased vaginal discharge or irritation, was noted during the period of cervical viral shedding.

Among the cohort the mean number of recurrences per patient was 4·3 (range 0–10). The frequency of recurrence ranged from 0·99 to 4·6 per 100 patient days with a mean of one recurrence every 53 days. Among those women studied within one year of their primary genital HSV infection, the frequency of recurrence was 2·2 per 100 patient days compared with 0·77 recurrences per 100 patient days in women with a history of HSV for longer than 24 months before being studied. No relationship between the frequency of recurrence and titre of complement fixing (CF) antibody to HSV was noted, and the patient (Case 3: Table 1) with the highest CF antibody titre (1:128) experienced the greatest number of recurrences. In addition, a rise or fall of more than 1 tube dilution in CF antibody titre in serum obtained at the beginning and end of the study did not occur in any patient. It is of interest that the only woman who experienced no recurrence was the only one initially infected with HSV-1. Although she was followed up twice weekly for only 13 weeks, less frequent follow-up revealed no symptomatic recurrences during the subsequent eight months.

The mean number of lesions during recurrences was 2·7 (range 1–12) and the mean duration from onset of symptoms to healing was six days (range 2–10). During symptomatic recurrences the duration of viral shedding, defined as the time from onset of lesions until the last day HSV was isolated from the lesions, was 1·9 days. As patients were seen at 3–4 day intervals, this figure represents a minimal estimate of the duration of viral shedding. Pain was present for an average of 5·2 days and itching 4·3 days. An increase in vaginal discharge was noted in 42% of the symptomatic recurrences, dysuria in 13%, and constitutional symptoms of malaise and fever were present in only one (4%) of the recurrences.

Before entering the study, four of the six women felt that their recurrences were precipitated by the onset of menses. When the date of onset of recurrences was analysed by time of menstrual cycle (Figure), no discernible relationship between menstrual period and onset of recurrent genital infection was present. Sixty-five per cent of recurrences began during midcycle, 23% during menses, and 11% in the five days preceding menses. It should be noted, however, that 24 of the 26 recurrences occurred in women taking oral contraceptives, and it is not known whether this mode of contraception affects the recurrence pattern of genital herpesvirus infection.

In addition, there was no obvious relationship between sexual activity and recurrent herpes virus infection in these women. All the women were sexually active. The mean number of days between last sexual contact and positive herpes cultures was 2·0 days compared with 2·7 days between last sexual contact and those visits not associated with recurrence ($P > 0{\cdot}05$ (t test)).

Discussion

In this study of women with recurrent genital herpes asymptomatic viral shedding accounted for 14% of

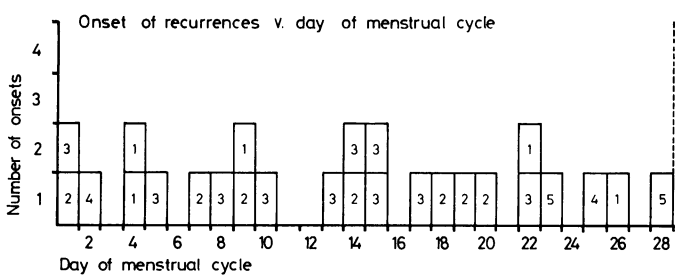

Figure *Onset of genital herpesvirus recurrence by day of menstrual cycle among women with recurrent disease*

the HSV culture-positive recurrences. In women with recurrent disease, both asymptomatic herpetic lesions and transient shedding of HSV from cervix or vulva without obvious herpetic lesions were documented. These data appear analogous to those of Douglas and Couch (1970), who reported that 2·2% of saliva specimens taken from asymptomatic patients with serological evidence of infection were positive for HSV (Douglas and Couch, 1970). Thus studies of the natural history and prevention of recurrent herpes should examine both symptomatic and asymptomatic disease.

The role that asymptomatic viral shedding may play in the transmission of genital HSV infections is unknown. Many patients presenting with initial genital HSV infections have sexual partners without recent signs or symptoms of infection. These contacts usually have serum antibody to HSV, but no clinically detectable HSV infections are present when they are examined. The data from this study suggest that these sexual partners may have had unnoticed lesions or transient shedding of HSV from the cervix or other sites without lesions.

Three of the six women with recurrent vulval disease shed HSV from the cervix at some time during the course of the investigation. It is possible that some women with recurrent genital herpes do not develop cervical recurrences and may have a risk of cervical carcinoma which differs from the risk seen in women with recurrent cervical shedding (Naib *et al.*, 1966; Rawls *et al.*, 1976).

The frequency of recurrence of genital disease was greater in women who had a history of genital herpes for less than 12 months before the beginning of the study (2·22 recurrences per 100 patient days) than in those with genital HSV of more than two years' duration (0·77 recurrences per 100 patient days). Further analyses of the frequency of recurrence in a larger number of intensively studied patients are needed to determine whether there is a decrease in the rate of shedding of HSV or a change with time in the pattern of symptoms associated with recurrence.

While all six women claimed that their herpetic recurrences were related to either menses or sexual activity, no discernible patterns between menses or sexual intercourse and the onset of recurrences were found. Fifteen recurrences began during days 7–21 of the cycle, and 12 recurrences began in the two weeks before and including the menses.

In previous studies the frequency of recurrence of genital herpes was found to be greater in men than women (Corey *et al.*, 1976; Vontver *et al.*, 1978). Whether this increased frequency of recurrence in men is due to a difference in the rate of viral shedding of HSV in men compared with women or if self-detection of trivial herpetic lesions is easier in men than in women remains unknown. Similar studies are needed in men to investigate the anatomical site, frequency, duration, and potential transmissibility of asymptomatic HSV shedding.

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